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Identification of a predominant COPD phenotype in clinical practice

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Summary
Background: Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation caused by small airways increased resistance and/or terminal airspaces emphysematous destruction. Spirometric detection of not fully reversible airflow limitation unifies under the acronym COPD, a spectrum of heterogeneous conditions, whose clinical presentations may be substantially different. In a cross-sectional study we aimed to ascertain whether COPD phenotypes reflecting different mechanisms of airflow limitation could be clinically identified.
Methods: Multidimensional scaling was used to visualize as a single point in a two-dimension space the multidimensional variables derived from each of 322 COPD patients (derivation set) by clinical, functional, and chest radiographic evaluation. Cluster analysis assigned then a cluster membership to each patient data point. Finally, using cluster membership as dependent variable and all data acquired as independent variables, we developed multivariate models to prospectively classify another group of 93 COPD patients (validation set) in whom high-resolution computerized tomography (HRCT) density parameters were measured.
Results: A multivariate model based on nine variables acquired from the derivation set by history (sputum characteristics), physical examination (adventitious sounds, hyperresonance), FEV_1/VC, and chest radiography (increased vascular markings, bronchial wall thickening, increased lung volume, reduced lung density) partitioned the validation set into two groups whose clinical, functional, chest radiographic, and HRCT characteristics corresponded to either an airways obstructive or a parenchymal destructive COPD phenotype.

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Conclusion: Patients with COPD can be assigned a clinical phenotype reflecting the prevalent mechanism of airflow limitation. The standardized identification of the predominant phenotype may permit to clinically characterize COPD beyond its unifying spirometric definition.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by expiratory airflow limitation caused by increased resistance of the small airways and/or increased compliance of the lung as a result of emphysema. The volume of air that can be expired within 1 s after the beginning of a forced expiration (FEV_1) is the hallmark of COPD because it is affected by inflammation and remodeling of the small airways as well as by emphysematous destruction of the terminal airspaces. Spirometric detection of not fully reversible airflow limitation unifies under the acronym COPD, a spectrum of heterogeneous conditions, whose clinical presentations may be substantially different.

Forty years ago Burrows et al. described the distinctive clinical, functional, radiological, and pathological characteristics of the emphysematous and bronchial types of chronic airways obstruction.[1] The terms *type A* and *type B* introduced to empirically differentiate COPD patients with the *emphysematous* type from those with the *bronchial* type of chronic airways obstruction[1] are no longer in use because a direct association between clinically defined types and lung pathologic findings, such as centriacinar and panacinar emphysema, has never been demonstrated.[2] Coexistence in the same patient of centriacinar and panacinar emphysema was indeed often found.[2]

However, as it has recently emphasized,[3–7] the current tendency to lump a variety of conditions under the acronym COPD may potentially blur important distinctions that could be useful in clinical practice to improve the understanding of the natural history of the disease and to focus treatment strategies for different COPD phenotypes.

Aim of this research was to ascertain whether in a large series of COPD patients it could be possible to identify subgroups whose clinical, functional, and radiological characteristics could enable to classify them as specific phenotypic presentations.

Methods

Subjects

From January 5 to December 31, 2004, we enrolled 415 consecutive COPD outpatients (83 females) with mild to severe airflow limitation to derive clinical, functional, and radiological characteristics that could represent the broad spectrum of COPD presentations.[8] Study enrollment was based on stability of clinical conditions within 2 months, availability of chest radiography within 1 week, and patient's willingness to participate. The institutional review board approved the study. Informed consent was obtained from all participants.

Clinical evaluation

Patients were visited by six chest physicians who worked independently on daily shift so as to cover 6 days a week. Visit consisted in a thorough clinical history with administration of the Medical Research Council questionnaire for the assessment of dyspnea severity,[9] physical examination,[10–13] and evaluation of chest radiography (Table 1). Physicians participating in the study had been previously trained to detect the radiographic findings reported in Table 1 by a set of representative films.[14,15] Table 1 was used as reading table to standardize the interpretation. Interobserver agreement in detecting the radiographic findings listed in Table 1 was tested using the chest radiographs of the first 100 patients enrolled.

Pulmonary function studies

Static and dynamic lung volumes and single breath diffusing capacity (DL_{CO}) were measured by a mass-flow sensor (V6200 Autobox Body Plethysmograph; Sensor Medics, Yorba Linda, CA) according to standard methodology.[16,17] Arterial blood gases were measured by a blood gas analyzer (ABL730; Radiometer, Copenhagen, Denmark). For each patient, the severity of COPD was graded according to the classification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[18]

Spirometrically gated high-resolution computerized tomography (HRTC)

Ninety-three among the 415 patients also underwent spirometrically gated HRCT (Somatom Plus; Siemens, Erlangen, Germany) to measure quantitative lung density parameters and served to prospectively validate the phenotype classification process. There were no pre-established selection criteria to perform the HRCT study and to include these patients in the validation set except for the clinician's perceived clinical utility of the examination to exclude concomitant disease. HRCT was obtained at predefined inspiratory lung volume to avoid the influence on density measurements of different lung inflation levels during scanning.[19] Patients breathed through a spirometer (Micromedical Instruments, Rochester, UK) connected to the scanner and performed reproducible vital capacity (VC) maneuvers. Subsequently, the airflow through the spirometer was interrupted at 90% of VC by a shutter triggering the scanner to acquire images at three levels (carina, 5 cm above, 5 cm below). Frequency histograms of lung attenuation values of each section were averaged[20] to derive X-ray mean attenuation, as overall assessment of lung density, and percentage area with X-ray attenuation values below −950

Table 1 Variables derived from clinical history, physical examination, and chest radiography in 415 patients with COPD.

Clinical history*	Physical examination*	Chest radiography*
Cough	Cyanosis	Increased vascular markings
Absent	Pursued lips breathing	• Vascular prominency
Occasional	Neck veins dilatation	• Blurred margins
Chronic	Hypertrophy of accessory muscles of respiration	• Increased tortuosity
	Barrel chest	
Sputum	Hoover's sign‡	Reduced vascular markings
Occasional	Peripheral oedema	• Vascular deficiency
Chronic	Chest hyperresonance	• Loss of side branches
Purulent	Reduced breath sounds	• Reduced sinuosity
	Adventitious breath sounds§	
MRC dyspnea scale†		Interstitial changes
None		• Poorly defined micronodulation
Slight		• Lobular atelectasis
Moderate		• Mucus filled acini
Severe		
Very severe		Reduced lung density
		• Loss of normal background pattern
		• Increased lucency
		• Widening of peripheral clear zone
		Increased lung volume
		• Flattened emidiaphragms
		• Increased retrosternal space
		• Enlarged intercostal spaces
		Bronchial wall thickening
		• Wall thickening of perihilar bronchi seen end-on or longitudinally
		• Visibility of the wall of small bronchi normally not seen

*Variables derived from clinical history, physical examination and chest radiography were entered in the statistical analysis as 1 when present or 0 when absent. A radiographic variable was considered to be present when at least one of the related specific findings was detected.

†Dyspnea on effort has been scored into five categories according to the Medical Research Council (MRC) dyspnea scale. None: not troubled by shortness of breath except with strenuous exercise; slight: troubled by shortness of breath when climbing a flight of stairs, hurrying on the level or walking up a slight hill; moderate: walks slower than people of the same age on the level because of shortness of breath; severe: stops for breath after walking about 100 yd or after a few minutes on the level; very severe: too breathless to leave the house or breathless when dressing or undressing.

‡Paradoxical inspiratory indrawing of the lateral rib margin (due to direct traction by flattened diaphragm on the lateral rib margin).

§Wheezes, crackles, ronchi.

Hounsfield units (HU), as index of emphysema extent.[21] The HRCT study was then completed according to the clinical needs of individual patients.

Data analysis

This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[22]

To delve into our large dataset with an unbiased approach, instead of using hypothesis-testing procedures by classic statistical methods, as in logistic or discriminant analysis, we explored the relationship among the whole set of variables by an undirected data driven approach. In particular, to globally explore the dataset considering all parameters at the same time we used the method called multidimensional scaling.[23] The analysis of multivariate data is indeed rendered difficult from the inability to plot and visualize the structure of multidimensional data. Multidimensional scaling allows to represent multivariate data points in a lower dimensional space allowing visual inspection of the whole dataset and to identify the presence of subsets of aggregation in the whole set of categorical (Table 1) and continuous (Table 2) variables derived from 322 of 415 patients (derivation set). All variables derived from each patient were thus represented as a single data point with two coordinates (principal coordinates I and II).

Table 2 Anthropometric, smoking, functional, and HRCT densitometric characteristics of 415 patients with COPD.

	Group of derivation of the classification variables (derivation set) $n = 322$, 66 females	Group of prospective validation (validation set) $n = 93$, 17 females	
	Mean (S.D.)	Mean (S.D.)	*P*
Age (year)	69 (7.7)	63 (8.0)	<0.001
BMI	26.5 (4.6)	25 (4.1)	NS
Pack/years	50 (30.8)	50 (37)	NS
FVC%	85 (18)	85 (22)	NS
FEV_1%	62 (19)	53 (21)	<0.001
FEV_1/VC	52 (12)	43 (13)	<0.001
FRC%	121 (30)	142 (33)	<0.001
RV%	136 (39)	162 (49)	<0.001
TLC%	105 (16)	116 (15)	<0.001
DL_{CO}%	72 (23)	70 (24)	NS
pH	7.42 (0.03)	7.41 (0.02)	NS
PaO_2 (mmHg)	74 (9.3)	72 (9.0)	NS
$PaCO_2$ (mmHg)	40 (4.2)	40 (4.4)	NS
PI (% lung area)	–	22 (11)	–
MLA (HU)	–	−880 (22)	–

HRCT: high-resolution computerized tomography; %: percent of predicted value; HU: Hounsfield units; BMI: body mass index; pack/years: number of daily cigarettes smoked *x* number of years of smoking/20; FVC: forced vital capacity; FEV_1: forced expiratory volume in the 1st second; VC: slow vital capacity; FEV_1/VC: Tiffeneau index; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; DL_{CO}: single-breath diffusing capacity for carbon monoxide; pH: negative logarithm of H^+ concentration; PaO_2: O_2 partial arterial tension; $PaCO_2$: CO_2 partial arterial tension; PI (% lung area): relative lung area with attenuation values below −950 HU for scans at 90% of VC; MLA: mean computerized tomography lung attenuation for scans at 90% of VC.

Cluster analysis[24] was then applied to segment the whole set of data points into relatively homogeneous subgroups. The clusters optimum number was selected according to the average silhouette width (ASW) value, a dimensionless number that must be higher than 0.25 to define the presence of a reliable clustering structure in the dataset.[25] A clustering algorithm[26] assigned to each patient data point a membership in one of the identified clusters.

A prospective classification model was subsequently developed by multiple linear regression using all parameters as independent variables and the patients cluster membership as dependent variable. The model with the highest discriminating power and the lowest number of variables, selected by multiple analysis of variance[27] in the 322 patients of the derivation set, was used to prospectively classify the 93 patients of the validation set.

The classification obtained by applying the same model to the whole sample of 415 patients was compared with GOLD stages of COPD severity.

Interobserver agreement in detecting the radiographic findings was assessed by *k* statistics. Student's *t*-test, Mann–Whitney test, and Fisher's exact test were used to compare continuous and categorical variables between the different COPD subgroups identified. Data are reported as mean ± S.D. Significance was set at $p<0.05$. Data analysis and statistics were performed using GraphPad Prism (version 3.02; San Diego, CA), S-Plus 2000 (Mathsoft, Cambridge, MA), SPSS/PC WIN 11.5.1 (SPSS, Chicago, IL), Mathcad (version 2001; Mathsoft), and C++ programming language.

Results

The anthropometric, smoking, and functional characteristics of the 322 patients of the derivation set and of the 93 patients of the validation set included in the study are reported in Table 2. Spirometrically gated HRCT densitometric measurements are reported for the 93 patients of the validation set. The latter were significantly younger, more obstructed, and hyperinflated with respect to the 322 patients from which the classification variables were derived. Among the whole series of 415 patients 68 (16%) were classified as GOLD 1 (mild COPD), 207 (50%) as GOLD 2 (moderate COPD), 113 (27%) as GOLD 3 (severe COPD), and 27 (7%) as GOLD 4 (very severe COPD). The validation set had a significantly higher prevalence of patients that, according to the GOLD classification, were staged as severe or very severe COPD (51% of the patients in the validation set versus 29% of the patients in the derivation set).

Interobserver agreement in detecting the radiographic findings of Table 1 ranged from moderate ($k = 0.59$ for interstitial changes) to very good ($k = 0.87$ for increased lung volume).

Figure 1 (left panel) shows the results of the application of multidimensional scaling to the 322 patients included in the derivation set. Visual inspection reveals the presence of two partially overlapping subsets of aggregation. One subset had negative values along principal coordinate I and higher dispersion of data points with respect to a second subset with positive values of principal coordinate I.

Figure 1 (right panel) shows the results of cluster analysis. The highest value of ASW (ASW = 0.32) was obtained when

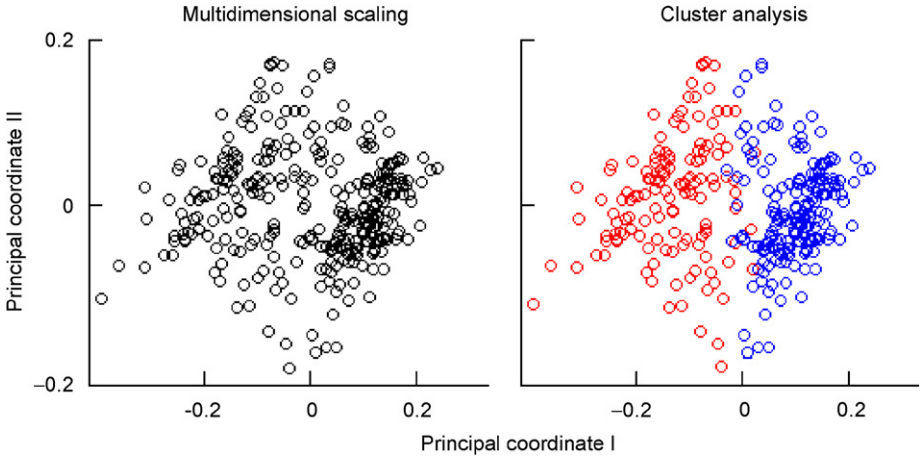

Figure 1 Left panel: two-dimensional graph obtained from the application of multidimensional scaling to the original multidimensional set of heterogeneous parameters (categorical and continuous; listed in Tables 1 and 2) derived from 322 patients with COPD. Each point of the graph represents the combination of all parameters (categorical and continuous) of each patient defined by two coordinates (principal coordinate I and II). Right panel: partitioning in two clusters of the whole dataset. Each patient data point is assigned a cluster membership (red or blue open circles) by a clustering algorithm.

Table 3 Multivariate regression model.*

Variables	Coefficients†
Occasional sputum	0.0644
Purulent sputum	−0.0211
Increased vascular markings	−0.0938
Bronchial wall thickening	−0.0566
Reduced lung density	0.1250
Adventitious breath sounds	−0.0281
Chest hyperresonance	0.0596
FEV_1/VC	−0.0011
Increased lung volume	0.0529
Constant	0.5060

*The model with the lowest number of variables and the highest discriminating power to assign a cluster membership to each of the 322 patient of the derivation set.

†For the prospective classification of patients, the coefficients were multiplied by 0 or 1 according to the presence or absence of the relative categorical variable. In the case of FEV_1/VC (ratio of forced expiratory volume in the first second over slow vital capacity), the coefficient was multiplied for the actual value of the continuous variable.

considering two as the optimum number of clusters within the series of patients data points. The two clusters identified had only slight overlap.

The multiple regression model, developed by using as independent variables all clinical, functional, and radiographic data acquired in the 322 patients, defined the previously determined cluster membership of the patients' data points with great accuracy ($R^2 = 0.92$). The simplest model, obtained by multiple analysis of variance (Table 3), consisted of nine out of the original variables and accounted for 91% of the variance in defining the cluster membership of each patient ($R^2 = 0.91$). Among the selected variables four were derived from history and physical examination, four from chest radiography, and one from functional evaluation. The selected variables were weighed by the relative coefficient (Table 3) and linearly combined to obtain scores for the classification of the 322 patients of the derivation set and for the prospective classification of the 93 patients of the validation set.

Figure 2 shows the bimodal shape of the probability density curves of the classification scores of the 322 patients used to develop the model and of the 93 patients used for its prospective validation. Since the lowest value of the probability density curve for the 93 patients of the validation set was at a score of 0.56, this figure was used as the cut-off value to subdivide these patients into two subsets: patients with a score higher than 0.56 (Group A, $n = 42$, mean score $\pm$ S.D. $= 0.69 \pm 0.06$) and patients with a score equal or lower than 0.56 (Group B, $n = 51$, mean score $\pm$ S.D.: 0.38 ± 0.09). Both groups had normally distributed classification scores and showed only marginal overlap (Group B: mean score+2 S.D. $= 0.56$; Group A: mean score-2 S.D. $= 0.57$) with only 19 (20%) of the 93 patients classified with scores comprised between 0.47 (Group B: mean score+1 S.D.) and 0.63 (Group A: mean score-1 S.D.). The two subsets of the 93 patients differed significantly for the vast majority of the categorical and continuous variables considered in the study (Table 4).

The comparison between GOLD stages of COPD severity and the distribution of the classification scores obtained in the 415 patients by application of the multivariate regression model (Table 3) is reported in Figure 3. The box and whisker plot (left panel) shows that patients with mild or moderate COPD (GOLD 1 and 2) have significantly lower ($p < 0.001$) classification scores than patients with severe or very severe COPD (GOLD 3 and 4). The right panel in Figure 3 shows that, using the score cut-off value of 0.56 to subdivide patients according to the predominant COPD phenotype, patients staged as GOLD 1 and 2 have, indeed, a higher probability ($p < 0.001$) than patients staged as GOLD 3 and 4 to be classified with the lower scores compatible with a bronchial clinical phenotype. However, patients staged as

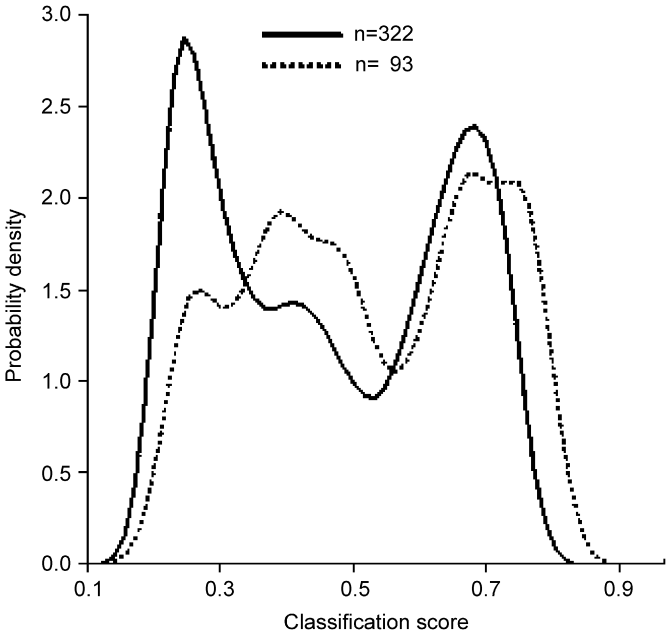

Figure 2 Probability density curves of the classification scores obtained from the application of the multivariate regression model reported in Table 3 to the 322 patients with COPD from whom the variables were derived (solid curve) and to the 93 patients used as a validation set in whom the model was prospectively applied (dashed curve).

GOLD 3 and 4 had equal probability of being classified by the multivariate regression model with scores compatible with either COPD phenotype.

Discussion

The main finding of this study is that a classification model developed from unsupervised and prospectively validated analysis can identify, along a continuous spectrum of clinical presentations, two distinct phenotypes of patient with not fully reversible chronic expiratory airflow limitation. The subgroups specific findings identified by the objective data driven analysis, although not specified in advance on the basis of differences on which the subgroups were expected to differ, do present definite biologically plausible differences.

With respect to Group B, patients of Group A were mainly characterized at clinical history by absent or occasional non-productive cough; at physical examination they were thinner, had more often pursued lips breathing, hypertrophied neck muscles, and chest inspiratory indrawing; the chest wall digital percussion generated high intensity sounds and at auscultation their breath sound was of low intensity. At functional evaluation they showed more marked increase in total lung capacity associated to a definite impairment of lung diffusing capacity; indexes of expiratory airflow limitation and hyperinflation were more severely altered. They had chest radiographic evidence of increased lung volume, reduced lung density, and attenuated vascular markings resulting on HRCT as reduced mean lung attenuation and increased percentage of lung area with density values compatible with emphysema. In general, this subgroup comprehends patients who present clinical, functional, and radiological data concurring to characterize them as being predominantly affected, to a various extent, by an *emphysematous* clinical phenotype of COPD.

Group B patients were more often characterized by a clinical history of chronic productive cough; they lacked most physical signs displayed by Group A patients, and at auscultation had more often adventitious breath sounds. Their chest films showed increased bronchial and vascular markings together with increased prevalence of interstitial changes compatible with chronic lung inflammation resulting on HRCT as relatively higher values of mean lung attenuation. On HRCT they also had a lower percentage of lung area with density values compatible with emphysema. In general, this subgroup comprehends patients who present clinical, functional, and radiological findings concurring to characterize them as being predominantly affected, to a various extent, by a *bronchial* clinical phenotype of COPD.

Although each patient might present, along the continuous bimodal spectrum of clinical presentations (Figure 2), a particular pattern of combination of clinical, functional, and radiological findings, one of the two clinical phenotypes was usually predominant even in most patients with an intermediate classification score. In the process of identifying the predominant COPD phenotype, besides clinical and functional data, a relevant role was played by conventional chest radiography whose findings were confirmed by spirometrically gated HRCT quantitative data.

Burrows et al. showed that a radiographic pattern of peripheral vascular attenuation without associated chronic inflammatory changes was highly correlated with the grade of *post-mortem* anatomical emphysema.[1] Besides chest radiography, the Burrows' study showed that the *post-mortem* grade of anatomical emphysema was positively predicted by reduced diffusing capacity and increased total lung capacity, and negatively predicted by increased sputum volume and increased $PaCO_2$.[1] Physical examination was not

Table 4 Variables significantly different in two subsets of 93 COPD patients (validation set) identified according to the scores derived from the multivariate regression model.

	Group A ($n = 42$), score > 0.56	Group B ($n = 51$), score $\leqslant 0.56$	
	Mean (S.D.)	Mean (S.D.)	P^*
Continuous variables			
BMI	24 (3)	27 (4)	<0.001
FEV_1%	45 (19)	59 (21)	<0.001
FEV_1/VC	38 (12)	48 (12)	<0.001
FRC%	158 (36)	129 (23)	<0.001
RV%	184 (56)	145 (34)	<0.001
TLC%	122 (16)	110 (12)	<0.001
DL_{CO}%	56 (24)	82 (17)	<0.001
PI (% lung area)	30 (11)	16 (7)	<0.001
MLA (HU)	−893 (20)	−874 (20)	<0.001
Categorical variables	Prevalence (%)	Prevalence (%)	$P^\dagger$
Absent cough	43	6	<0.001
Occasional cough	19	10	<0.001
Chronic cough	38	84	<0.001
Occasional sputum	62	10	<0.001
Chronic sputum	9	31	<0.001
Purulent sputum	29	59	<0.001
Pursued lips breathing	31	8	<0.01
Hypertrophy of accessory muscles	26	6	<0.001
Hoover's sign	19	4	<0.05
Chest hyperresonance	81	33	<0.001
Reduced breath sounds	93	73	<0.05
Adventitious breath sounds	50	76	<0.01
Increased vascular markings	2	82	<0.001
Reduced vascular markings	79	16	<0.001
Interstitial changes	5	29	<0.005
Reduced lung density	95	29	<0.001
Increased lung volume	95	53	<0.001
Bronchial wall thickening	12	90	<0.001

See Table 2 for abbreviations.
*Student's *t*-test.
†Fisher's exact-test.

considered. Apart from $PaCO_2$, which did not show significantly higher values in patients with a predominant bronchial phenotype (Table 4), our study confirms the results obtained by Burrows et al.[1] The different relevance of $PaCO_2$ in distinguishing the two phenotypes may be ascribed to differences between our patients and those examined in the Burrow's study who had more severe conditions of respiratory insufficiency (mean $PaCO_2 = 54$ mmHg, mean $FEV_1 = 0.67$ l, FEV_1/VC always lower than 50%).

There is increasing evidence that HRCT may provide information *in vivo* on the pathologic changes occurring in patients with COPD.[28] The complexity and heterogeneity of the pathological processes underlying COPD clinical presentation in primary care has been demonstrated in a large series of patients studied by HRCT after an acute exacerbation.[29] Other studies in smaller series have shown that among COPD patients those with emphysema documented by HRCT had greater expiratory airflow limitation, hyperinflation, and lower diffusing capacity.[30,31] Furthermore, a chest radiographic score of chronic inflammatory changes showed a negative correlation with the HRCT score of emphysema, suggesting that the features of conductive airway inflammation are predominant in COPD patients with no or with only trivial emphysema.[30] Accordingly, O'Donnell et al. found that sputum neutrophil counts in COPD was closely associated with airway dysfunction, but not with the severity of emphysema as assessed by HRCT and lung diffusing capacity.[32]

The finding of an increased prevalence of a bronchial phenotype among patients with mild and moderate disease, as shown by the comparison between the distribution of the classification scores and GOLD stages of COPD, is in keeping with previous reports showing that patients with an HRCT determined emphysema phenotype have more severe clinical presentations of COPD.[30,31] Although it is difficult from the present cross-sectional study to exclude

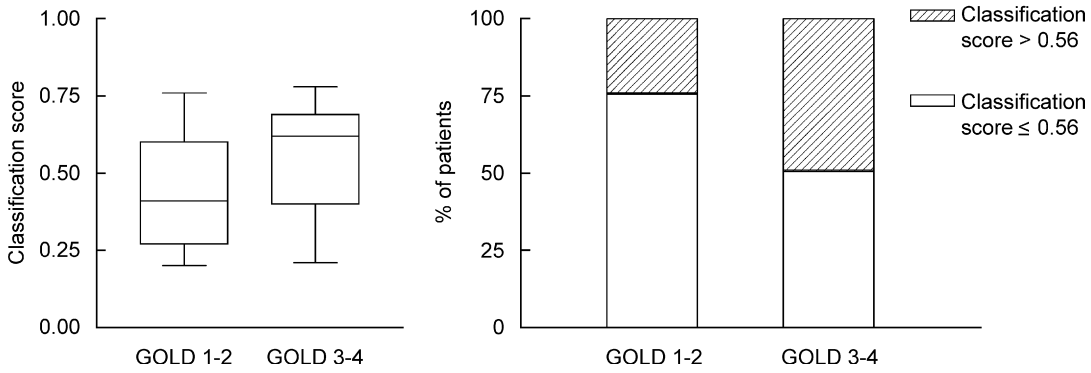

Figure 3 Left panel: box and whisker plot of the classification scores attributed by the multivariate regression model reported in Table 3 to the whole sample of 415 COPD patients as a function of the GOLD stage of COPD severity. Line in box: 50th percentile (median); limits of box: 25th and 75th percentiles; whiskers: minimum and maximum. No significant difference (Mann–Whitney test) in the classification scores was found either between GOLD 1 and 2 stages or between GOLD 3 and 4 stages, while the classification scores of GOLD 1 and 2 stages were significantly different ($p<0.001$) from those of GOLD 3 and 4 stages. Right panel: histograms representing the percent distribution, according to GOLD stages, of the 415 COPD patients classification scores above or below the value of 0.56.

the effects of COPD progression on our findings, the observed balanced prevalence of the two phenotypes among patients with GOLD stages 3 and 4 may indicate that disease progression does not wipe out the original clinical phenotype.

Most HRCT studies in COPD have dealt with the severity and extent of emphysema with little attention to the airway changes. Recently, it has been shown that the combination of a measure of airway thickening with the extent of emphysema improved the estimate of pulmonary function abnormalities and could be useful to differentiate COPD patients with primarily parenchymal disease from those with airway pathology.[33–36] In the same line of evidence, COPD patients with a clinical diagnosis of chronic bronchitis had on HRCT increased bronchial wall thickness with respect to COPD patients without clinical findings compatible with chronic bronchitis.[35] The latter, on the other hand, had on HRCT a more severe reduction of X-ray mean lung attenuation and a higher percentage of lung area with attenuation values below −950 HU, were more obstructed and hyperinflated, and had lower diffusing capacity.[35] A correlation between bronchial wall changes on HRCT and functional indexes of obstruction was found only in patients with clinical findings compatible with chronic bronchitis.[35] Furthermore, it has been shown that COPD patients who present airway wall thickening on HRCT have greater reversibility of airflow obstruction in response to inhaled bronchodilators and corticosteroids than those with emphysema without bronchial wall thickening.[36] These data, taken together, suggest that expiratory airflow limitation is mainly associated to airways pathology in COPD patients with predominant features of chronic bronchitis, while it is mainly associated to parenchymal destructive changes in COPD patients with predominant features of emphysema.

The series of patients from which, in this study, the differentiating variables have been derived, could be considered somewhat representative of the whole spectrum of COPD clinical presentations, as it may be indicated by the results of the prospective validation in a group of patients with different age and COPD severity. On the other hand, the different clinical characteristics of patients enrolled in the validation set with respect to those of the derivation set may have influenced the distribution of the classification scores and, consequently, the determination of the cut-off value used to subdivide the patients of the derivation set into two subgroups (Figure 2). This study design limitation could also have affected the observed distribution of patients according to GOLD classification of COPD severity (Figure 3). A further limitation of this work is that the cross-sectional design of the study does not allow us to ascertain whether patients with different phenotypes of COPD could have different outcomes. It appears then that further studies, possibly longitudinal and including greater samples of patients, are needed to confirm the results obtained in the present investigation.

In conclusion, it appears that each patient with COPD, although being the individual clinical expression of a wide and continuous spectrum of pathologic changes (different lesions may coexist) causing expiratory airflow limitation,[37] could be classified as being affected by predominant airway disease or by predominant parenchymal destructive changes. The identification of the predominant COPD phenotype by few findings derived from clinical and functional evaluation, as well as by standardized reading of conventional chest radiography may offer the opportunity to characterize this heterogeneous disease beyond its unifying spirometric definition. This may well impact on understanding the results of pharmacologic trials,[38] on clinician's approach to patient treatment, and on deeper knowledge of COPD natural history.

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Conflict of interest statement

None of the authors had financial or personal relationships with other people or organizations that could inappropriately influence this work.

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Appendix A. Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2007.10.019.

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